IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **FERREE** **Serial No.: 10/630,445** Filed: July 30, 2003 For: METHODS FOR TREATING A DEFECT IN THE ANNULUS FIBROSIS (as amended)	Group Art Unit: 3731 Examiner: Uyen T. Ho

DECLARATION OF BRET FERREE, M.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Bret Ferree, M.D., do declare that:

1. I am a Board Certified Orthopedic surgeon specializing in spinal surgery. I am also a voluntary Assistant Professor at the University of Cincinnati. I received an M.D. from the University of Cincinnati College of Medicine (Cincinnati, Ohio) in 1986. I also completed a fellowship in the Department of Orthopedic Surgery at Tufts Medical School, New England Baptist Hospital (Boston, Massachusetts). I am the inventor of this application and President and Chief Executive Officer of Anova Corporation, assignee of the above-referenced application. I have a financial interest in this application.

2. I have reviewed U.S. Application Serial No. 10/630,445 and the pending claims.

3. I have reviewed the following references.

- Bao et al. U.S. Patent No. 6,224,630 "Implantable Tissue Repair Device" (Exhibit A)
- Ruiz U.S. Patent No. 5,976,174 "Medical Hole Closure Device and Methods of Use" (Exhibit B)
- Diaz U.S. Patent No. 5,690,674 "Wound Closure with Plug" (Exhibit C)
- Bao et al. U.S. Patent No. 5,192,326 "Hydrogel Bead Intervertebral Disc Nucleus" (Exhibit D)
- Eberbach U.S. Patent No. 5,116,357 "Hernia Plug and Introducer Apparatus" (Exhibit E)
- Flament et al. U.S. Patent No. 6,180,848 "Prosthesis Obturating Device for the Obturation of a Hernial Canal" (Exhibit F)

4. In my capacity as an orthopedic surgeon specializing in spinal surgery, I have performed over 1,500 surgeries to repair disc herniations. Disc herniations occur when the nucleus pulposus extrudes through an opening in the anulus fibrosus (also sometimes referred to as "annulus fibrosis"). The posterior and posterior-lateral portions of the anulus fibrosus are most susceptible to herniations. Therefore, the extruded nucleus pulposus often impinges on nerve roots in the spine, as seen in the figures below.

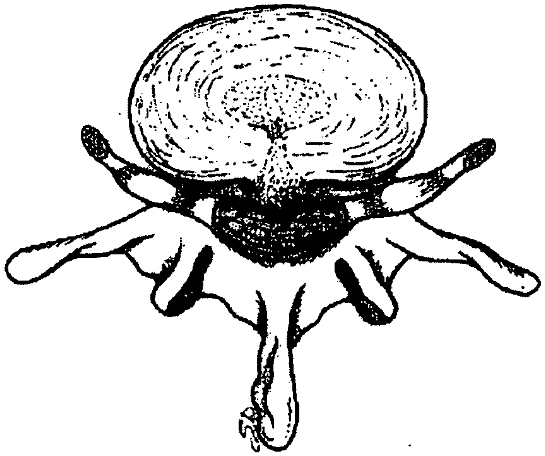

Fig. 5.18. *Midline disc herniation.*

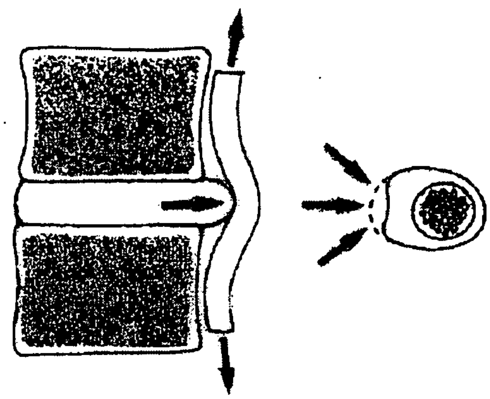

Fig. 6.3. *Compression of the radicular nerve by herniated disc. The herniation causes an asymmetric compression of the radicular nerve, whereby the nerve fibers are dislocated towards the opposite zone with respect to the applied force. Moreover, disc herniation produces tensile stresses in the zone of the radicular nerve above and below the contact area.*

Postacchini, F., LUMBAR DISC HERNIATION, Springer-Verlag/Wien, 1999, pages 108-109 and 140. (Exhibit G)

5. One of the main purposes of disc herniation repair is to alleviate pain associated with the pinched nerve. Therefore, an orthopedic surgeon seeking to close the opening in the anulus fibrosus would not implant any device that would impinge on and compress nerves. Consequently, a surgeon would not look to references that describe implant devices with mechanisms and shapes that might contact or migrate toward the posterior of the anulus fibrosus and thereby compress or injure the delicate nerves that overly the posterior surface of the disc.

6. Claims 85-114 require implants that expand radially by reducing the length between the distal and proximal ends. This feature insures that the devices of the invention do not impinge on the nerves of the spine. In fact, the claimed devices move <u>away</u> from the nerves when they deploy.

a) Claim 85 requires that "the porous mesh expands radially by reducing the length between the distal and proximal ends."

b) Claim 99 requires that "the implant expands radially by reducing the length between the distal and proximal ends."

7. I understand the Examiner has taken the position that Bao et al. (U.S. Patent No. 6,224,630) describes all of the steps claimed except for the step of using a porous mesh having the configuration as claimed. I also understand the Examiner believes that "the porous mesh having configuration as claimed are well known in the art of patching, closing wound," and provided several references in support of the allegedly "well-known" statement. (Office Action, page 2) For the reasons outlined below, a skilled orthopedic surgeon would not have looked to the implants described in the cited references for use in the method taught in Bao, U.S. Patent No. 6,224,630, because a skilled orthopedic surgeon would have concluded that each implant was not suitable for disc herniation repair.

8. Ruiz, U.S. Patent No. 5,976,174, is concerned with hole closure devices for use in treating cardiac septal defects. (See Abstract). As seen in Fig. 1B (reproduced below), the device is a "flexible tube that is inserted through the hole and then <u>radially expanded on either side of the hole</u>. Expansion of the ends of the tube causes a mid-region of the tube to contact and conform to the dimensions of the hole, and to exert a radial force along the edge of the hole, thereby sealing it." (emphasis added, Col. 2, lines 47-52)

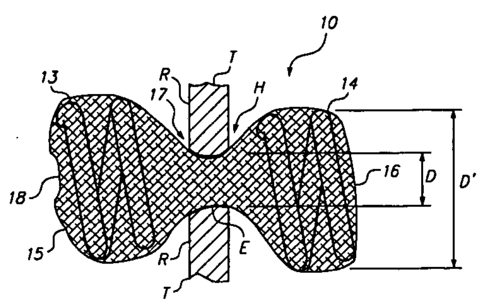

FIG. 1B

A surgeon would not use such a device for repair of a disc herniation because of the hourglass shape of the implant. The enlarged portion of the device, if used in a disc herniation procedure, would extend from the posterior side of the anulus fibrosus and would, in a majority of patients, compress or otherwise injure the delicate nerves that overly the posterior surface of the disc. Therefore, the Ruiz device would be rejected because the "cure" would result in the same problems originally caused by the herniated disc.

9. Further, the device described in Ruiz could not withstand the high pressures found in the intradiscal space, which are generally above 750 mmHg with normal activity and can be as high as 2.3 MPa (17,251 mmHg). (See, e.g., Wilke et al. "New *In Vivo* Measurements of Pressure in the Intervertebral Disc in Daily Life," Spine:24(8): 755-62, Table 1 (1999) (Exhibit H); see also Einhorn "Stability of a Mechanical Barrier Used to Seal Annular Defects." (Poster) Global Symposium on Motion Preservation Technology, Spinal Arthroplasty Society. New York (May 4-7, 2005) (Exhibit I) "intradiscal pressures as high as 330 psi have been reported") Intravascular pressure is on average 120 mmHg (systolic)/80 mmHg (diastolic), but can be as high as 300 mmHg (systolic)/160 mmHg (diastolic), which is far lower than 17,251 mmHg pressure in the intradiscal space. The Ruiz device is delivered percutaneously and therefore Ruiz's device must be thin and flexible in order to be manipulated through twists and turns in blood vessels before reaching the heart. The Ruiz device is therefore too thin and flexible to function in an intervertebral disc because it could not withstand the high pressures.

10. Diaz, U.S. Patent No. 5,690,674, describes an elastic, biodegradable plug with a proximal retainer and a distal retainer coupled by a waist that may be positioned to straddle a wound in a blood vessel wall. (See Abstract). "As illustrated in FIG. 10, the waist **130** [Fig. 1]

of the plug **100** couples the proximal retainer **110** and the distal retainer **120** such that the plug **100** may be positioned to straddle the wound in the vessel wall **410** with the waist **130** [Fig. 1] positioned in the wound of the vessel wall **410**." (Col. 3, lines 60-64).

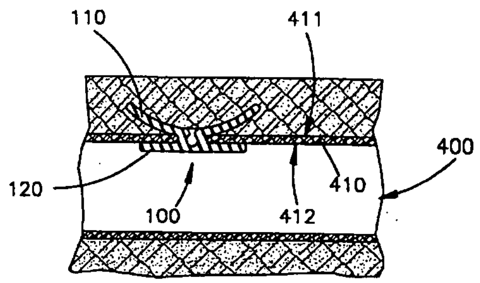

Fig.10

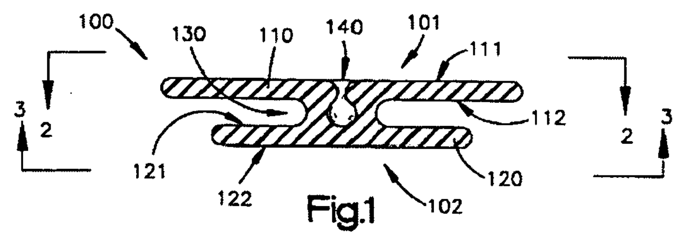

Fig.1

Like Ruiz, the Diaz device has an enlarged portion **110** that would, if the device were used to repair a ruptured disc, remain on the posterior side of the anulus fibrosus and curve outwardly in a posterior direction. The device would therefore, in a majority of patients, press against and injure the delicate nerves that overly the posterior surface of the disc.

11. The Diaz device also could not withstand the high pressures found in the intradiscal space, which are generally above 750 mmHg with normal activity and can be as high as 2.3 MPa (17,251 mmHg). The Diaz device is intended to withstand intravascular pressures, which are on average 120 mmHg (systolic)/80 mmHg (diastolic), but can be as high as 300 mmHg (systolic)/160 mmHg (diastolic), which is far lower than 17,251 mmHg pressure in the intradiscal space. The Diaz device is too thin and flexible to function in the intervertebral disc because it is not designed to withstand the high pressures.

12. Bao et al., U.S. Patent No. 5,192,326, describes a "prosthetic nucleus for implantation in the disc space after removal of a damaged or degenerated nucleus." (Abstract) The prosthetic nucleus is formed from a multiplicity of hydrogel beads. Bao teaches to partially

or totally replace the herniated nucleus with the prosthetic hydrogel nucleus. (See Col. 13, lines 56-60) The Examiner has cited Bao as teaching "a porous membrane that's expanded to seal a hole and prevent the escape of the nucleus through the defect." (Office Action, page 3) This statement is incorrect. Bao describes prosthetic nucleus implants designed to replace, not to prevent the escape of, the nucleus.

13. Bao describes using a membrane to encapsulate the prosthetic nucleus, which prosthetic nucleus is made of hydrogel beads. (See Col. 13, lines 38-45 "Hydrogel beads **100** are surrounded by a membrane **102** which may be made from nylon or dacron in woven form or may be made from various materials described below which produce the desired porosity. In using prosthetic nucleus **90**, the natural nucleus of a herniated disc as shown in FIG. 12 is removed via an opening **104**. The prosthetic nucleus **90** is then inserted through opening **104** in its dehydrated state as shown in FIG. 14." emphasis added) Bao teaches that the membrane retains the hydrogel beads, but the membrane and the beads do not retain the nucleus. Instead, Bao teaches to remove the nucleus. To the extent that any portion of the nucleus pulposus remains when the hydrogel is inserted, the Bao device does not retain the nucleus pulposus. Hydrogel nucleus replacement devices have been tried clinically. Not only have they been found to not contain the nucleus pulposus within the disc, the hydrogel has also been found to extrude from the disc. (See, e.g., Ray, C. D. Chapter 40. The Raymedica Prosthetic Disc Nucleus: An Update" EMERGING SPINE SURGERY TECHNOLOGIES. pages 583-591, 591 Corbin, T.P., ed. Quality Medical Publishing, Inc. 2006 (Exhibit J) "Initially, the device displacement rate was an unacceptable 37.3%, about two thirds of which required reoperation. This displacement, usually partial, was the single most important consideration during these trials, although no

patient had more than temporary root compression effects, much like a herniated disc.") Therefore, Bao does not describe a device that prevents escape of the nucleus pulposus because the nucleus pulposus has already been removed.

14. Moreover, the Bao device expands in all directions. Therefore the Bao device does not meet the requirement that "the implant expands radially by reducing the length between the distal and proximal ends." The device described in Bao '326 would be rejected by a skilled orthopedic surgeon as not applicable for closing a defect in the anulus fibrosus.

15. Eberbach, U.S. Patent No. 5,116,357, describes a device for repair of hernias including a plug positionable in an opening in the abdominal wall and a patch positionable over a weakened portion of the abdomen adjacent the opening. (See Abstract).

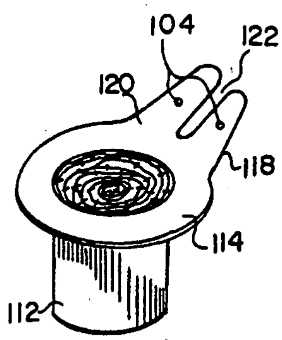

FIG. 16

Eberbach teaches to internally plug the weakened region and to patch all primary and secondary abdominal areas that are predisposed to hernias. (See Col. 2, lines 37-41). The approach of using a bulky patch and plug positioned on the outside of the defect would be rejected because it would, in a majority of patients, cause the same problems of compressing and injuring delicate nerves that overly the posterior surface of the disc.

16. Furthermore, Eberbach teaches that the patch can be made of "a surgically clean material which is durable, flexible, essentially inextensible, and resistant to corrosion from body fluids." (Col. 5, lines 34-37) Examples of materials are polypropylene and nylon. (See Col. 5, lines 34-43) A known problem with prosthetic materials such as polypropylene mesh is the development of adhesions. Macroporous polypropylene mesh was found to promote adhesion formation in a rabbit model. (See Matthews et al., "Assessment of Adhesion Formation to Intra-abdominal Polypropylene Mesh and Polytetrafluoroethylene Mesh," J. SURG. RES.: 114(2): 126-32 (2003) (Exhibit K)) Therefore, the Eberbach device would have been rejected by a surgeon exploring treatments for disc herniation because of the danger of adhesions forming on the outside of the anulus, which adhesions would tether the nerves to the disc, resulting in injury to the delicate nerves that overly the posterior surface of the disc during normal spine movement. (See, e.g., Einhaus, S.L. et al. "Reduction of Peridural Fibrosis After Lumbar Laminotomy and Discectomy in Dogs by a Resorbable Gel (ADCON-L)" Spine 22(13): 1440-47, 1440 (1997) (Exhibit L) "Estimations of the rate of unsatisfactory results after lumbar disc surgery range from 5% to 40% in the literature. Although the causes of the 'failed back surgery syndrome' can be multifactorial, many clinical investigators consider peridural fibrosis to be one of the major etiologies for this condition. These authors have hypothesized that the peridural scar interferes with the neuromechanics of the nerve root and dura during movement of the spine and limbs.")

17. Although "the contents of the abdominal cavity may be sufficient to apply adequate pressure to hold the patches in proper position," Eberbach also notes that his patch is secured to the outside of the abdomen using only staples or sutures. (See Col 10, limes 7-9). Intra-abdominal pressures range from 1.5 mmHg at rest to a maximum of 150 mmHg. (See

Morales-Conde, S. LAPAROSCOPIC VENTRAL HERNIA REPAIR, Springer Verlag France 2003, page 46) (Exhibit M) The Eberbach device could not withstand the high pressures found in the intradiscal space, which can exceed 2.3 MPa (17,251 mmHg), and therefore would be rejected as a proposed solution to disc herniation repair.

18. Flament, U.S. Patent No. 6,180,848, describes a device for obturating a hernial canal, the device having a first part extending through the hernial canal and a second part for covering the internal orifice of the hernial canal. (See Abstract)

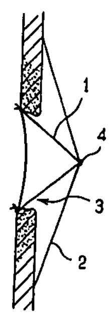

Fig. 2

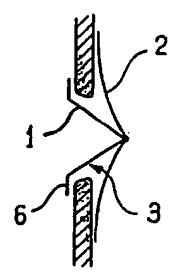

Fig. 3

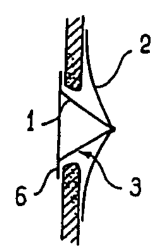

Fig. 4

Flament teaches that the portion of the device (numeral **1**) that obturates the hernial canal is either positioned at the superficial orifice of the canal (see Fig. 2 and Col. 3, lines 25-30), includes an additional base (numeral **6**) that bears on the outside margin of the wall of the hernial canal (see Fig. 3, Col. 3, lines 50-53), or includes an additional sheet (numeral **6**) that is fitted to the end of the device and is positioned outside of the hernial canal (see Fig. 4, Col. 3, lines 54-51).

19. None of the devices exemplified in Flament are positioned "distally beyond the outer layer in the annulus fibrosis," as required by the claims.. In fact, if used to repair an anulus, each would extend beyond the outermost layer of the anulus toward the nerves, i.e., toward the

left side of Figs. 2-4. In contrast, by requiring that the implant be advanced distally beyond the outer layer in the anulus fibrosus, the claimed invention allows the outer layer of the anulus fibrosus to act as a stabilizer and a cushion between the edges of the implanted device and the nerves. Cushioning and stabilizing are particularly important in light of the large compressive forces applied to the device in the intradisc space. Spinal devices are exposed to large extrusion forces from the nucleus pulposus and large axial compression forces from the vertebra above and below the device. It is imperative to keep the device from migrating even one millimeter towards the nerves. Compression on the sides of the portion of device 1 that obturates the hernial canal will tend to force that portion of the device out of the aperture and into what would be the nerves if the Flament device were used in a spinal application, as proposed in the Office Action.

20. I further declare that all statements made in this Declaration of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent and application involved in the present proceedings.

Dated: 9/25/06

Bret Ferree, M.D.